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10/650,326	08/28/2003	Keith A. Hruska	STK-P01-599	6882

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/650,326	HRUSKA ET AL.	
	Examiner	Art Unit	
	Christina Borgeest	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 April 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *56,69-71,76 and 78* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *56,69-71,76 and 78* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Formal Matters

The response filed 8 April 2009 is acknowledged. Claims 56, 69-71, 76 and 78 are under examination.

Rejections Withdrawn

Double Patenting

The rejection of claims 56, 71, 76 and 78 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-13 of U.S. Patent No. 6,677,432 in view of in view of London et al. (of record) and Vukicevic et al. (of record) is withdrawn in response to Applicants' explanation of the special characteristics of the mutant proteins recited in the claims of the '432 patent and that they do not render obvious the native morphogens of the instant claims.

The rejection of claims 56 and 69 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-13 of U.S. Patent No. 6,677,432 in view of in view of London et al. (of record) as applied to claims 56, 71-76 and 78 in the immediately preceding paragraphs and further in view of Vukicevic et al. and Salvetti (both of record) is withdrawn in response to Applicants' explanation of the special characteristics of the mutant proteins recited in the claims of the '432 patent and that they do not render obvious the native morphogens of the instant claims.

The rejection of claims 56, 71, 76 and 78 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-5 of U.S. Patent No. 6,846,906 in view of in view of London et al. (of record) and Vukicevic et al. (of record) is withdrawn in response to Applicants' explanation of the special characteristics of the mutant proteins recited in the claims of the '906 patent and that they do not render obvious the native morphogens of the instant claims.

The rejection of claims 56 and 69 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-5 of U.S. Patent No. 6,846,906 in view of in view of London et al. (of record) as applied to claims 56, 71-76 and 78 in the immediately preceding paragraphs and further in view of Vukicevic et al. and Salvetti (of record) is withdrawn in response to Applicants' explanation of the special characteristics of the mutant proteins recited in the claims of the '432 patent and that they do not render obvious the native morphogens of the instant claims.

The provisional rejection of claims 56, 71, 76 and 78 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 10 and 16-18 of copending Application No. 10/816,768 in view of in view of London et al. and Vukicevic et al (both of record) is withdrawn because the mutant proteins recited in the claims of the '768 application do not render obvious the native morphogens of the instant claims.

The provisional rejection of claims 56 and 69 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 10 and 16-18 of copending Application No. 10/816,768 in view of in view of London et al. (of record) as applied to claims 56, 71-76 and 78 in the immediately preceding paragraphs and further in view of Vukicevic et al. and Salvetti (both of record) is withdrawn because the mutant morphogens recited in the claims of the '768 application do not render obvious the native morphogens of the instant claims.

Rejections Maintained

Claim Rejections - 35 USC § 103

Note that Applicants' Arguments will be addressed at the end of the two rejections under 35 U.S.C. 103, since they are directed at both.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The rejection of claims 56 and 70-71, 76 and 78 under 35 U.S.C. 103(a) as being unpatentable over Sampath et al. (U.S. Patent No: 6,498,142, filed 6 May 1996—of record) and London et al. (Journal of hypertension. 1996; 14: 1139-46—of record) as set forth in previous Office actions (mailed 16 October 2008, 11 June 2007 and 21 September 2006) is maintained for reasons of record and the following. The claims are drawn to a pharmaceutical composition comprising a therapeutically effective amount of an ACE inhibitor and an OP/BMP morphogen, wherein the combination of said ACE inhibitor and BMP mrophogen is capable of inducing a synergistic effect on reducing proteinuria levels in a diabetic nephropathy model (as recited in claim 56) formulated with pharmaceutically acceptable salt, carrier, excipient or diluent (claim 76) wherein the morphogen is the polypeptide of SEQ ID NO: 3 (claim 70), or wherein the morphogen is a first polypeptide including at least a C-terminal cysteine domain of a protein selected from: a pro form, a mature form, or a soluble form of a second polypeptide, wherein said

second polypeptide is: OP-1, OP-2, OP-3, BMP2, BMP3, BMP4, BMP5, BMP6, or BMP9 (claim 71), in association with instructions for administering the composition to a mammal for treatment or prevention of chronic renal failure (claim 78—note that written instructions are not statutory subject matter in a patent, thus are given no patentable weight). Response to Applicants' arguments follows this section.

The rejection of claim 69 under 35 U.S.C. 103(a) as being unpatentable over Sampath et al. (U.S. Patent No: 6,498,142) and London et al. (Journal of hypertension. 1996; 14: 1139-46) as applied to claims 56 and 70-71, 76 and 78 in the immediately preceding paragraph and Salvetti (Drugs. 1990; 40: 800-28—of record) as set forth in previous Office actions (mailed 16 October 2008, 11 June 2007 and 21 September 2006) is maintained for reasons of record and the following. Claim 69 limits the ACE inhibitor to enalpril. Response to Applicants' arguments follows this section.

Response to Arguments

Applicants' make the same arguments against both rejections under 35 U.S.C. 103(a), thus for the sake of brevity, the arguments are addressed jointly below.

Applicants argue at p. 7, 2nd paragraph that nothing in Sampath, London, Ritz or de Zeeuw alone or in combination would lead the skilled worker to the claimed invention. Applicants further point out at p. 7, last paragraph through p. 8 1st and 2nd paragraphs that Sampath discloses only that OP-1 treatment resulted in overall improvement of renal tissue morphology, increased mesangial or perivascular thickening, decreased glomerular sclerosis and loop collapse, decreased presence of scattered sclerosis and microaneurysms and an increase in viable glomeruli and GFR compared to control. Applicants point out that improved glomerular filtration rate (GFR)

is not synonymous with improved proteinuria. Applicants argue that London teach only that ACE inhibitor treatment of patients with end stage renal disease (ESRD) improved blood pressure. In contrast, Applicants argue that the claims require the combination of the ACE inhibitor and BMP morphogen is capable of inducing a synergistic effect on reducing proteinuria levels in a diabetic nephropathy model. Applicants point out at the bottom of p. 8 where in the specification (p. 143, lines 6-10) that a showing of synergism can be found. Finally, Applicants argue at p. 11, 1st paragraph, that Salvetti does not teach or suggest that BMPs improve proteinuria, or combining BMPs with ACE inhibitors would have a synergistic effect on reducing proteinuria.

This argument has been fully considered but is not found persuasive. As Applicants point out in their response at p. 7, they are claiming a product (composition) ***not*** a method of reducing proteinuria levels in a diabetic neuropathy model. Sampath et al. disclose that OP-1 successfully attenuates renal failure in an art-accepted model for renal failure (column 29, lines 3-36). London et al. teach the administration of ACE inhibitors for the treatment of hypertensive subjects with end-stage renal disease (p.1140, left column, 3rd paragraph). Thus, both OP-1 and ACE inhibitors are used to treat the same patient population, which is patients with renal disease, as was indicated, for example at p. 6 of the previous Office action. This patient population is also specifically encompassed by the instant claims and specification. Both OP-1 and ACE inhibitors were known in the art cited by the Examiner to be used for the purpose of treating patients with renal disease.

Furthermore, the person of ordinary skill in the art would be strongly motivated to prescribe OP-1 and an ACE inhibitor to an individual with renal disease based upon the very teachings that Applicants cite. Even though the findings of Sampath do not specifically recite proteinuria, the condition of proteinuria, or albumin in the urine is a result of compromised glomeruli, as taught at paragraph [0580] of the specification:

> Proteinuria is an abnormally high amount of protein in the urine. Proteins in the blood, like albumin and immunoglobulin, help coagulation (clotting), balance bodily fluids, and fight infection. The kidneys remove wastes from protein-rich blood through millions of tiny filtering screens called glomeruli. Most proteins are too large to pass through the glomeruli into the urine. The glomeruli are negatively charged, so they repel the negatively charged proteins. Thus, a size and charge barrier keeps protein molecules from entering the urine. But when the glomeruli are damaged, proteins of various sizes pass through them and are excreted in the urine.

GFR and proteinuria are not synonymous, but they are related because GFR is a measure of the effectiveness of the glomeruli at filtering wastes out of the blood, thus is a measure of the glomeruli and proteinuria occurs as a result of damaged glomeruli. Furthermore, one of ordinary skill in the art, in this case, a physician or physician-scientist, upon reading Sampath would note that OP-1 decreases glomerular sclerosis and loop collapse, the presence of scattered sclerosis and microaneurysms and increases viable glomeruli and improves GFR. Thus, one skilled in the art would conclude that OP-1 would most likely improve glomeruli in patients with compromised glomeruli. Finally, with regard to London, renal disease and proteinuria are strongly causally associated with hypertension, as noted at paragraph [0583] of the specification: Hypertension and diabetes are the two biggest risk factors for proteinuria. Old age and weight gain also increase the risk. The following conditions cause proteinuria:... [0587] Hypertension." This is supported by Ritz and de Zeeuw (both of record; see p. 10 of the previous Office action for full discussion with citations), who teach that ACE inhibitors improve glomerular function and proteinuria. The person of ordinary skill in the art would be strongly motivated to prescribe an ACE inhibitor to persons with ESRD, as

noted in London. The art clearly teaches a nexus between renal disease and hypertension.

Applicants argue at p 9, 1st paragraph that based upon reading Ritz, the skilled worker would expect no more than an additive effect on proteinuria. In addition, Applicants argue at p. 9, 2nd paragraph that the case law relied upon by the Examiner regarding synergism (*In re Huellmantel* and *In re Meinhardt*—citations omitted) are inapposite, because in both cases the prior art taught or suggested synergism.

These arguments have been fully considered but are not found persuasive. As noted above, the person of ordinary skill in the art would be strongly motivated to prescribe OP-1 and ACE inhibitors to persons with renal disease. Applicants are not claiming a method, but rather a composition, and both of the agents that make up the claimed composition were taught in the prior art to separately be beneficial to patients with renal disease. It would have been obvious to one skilled in the art to combine the separate compounds into one composition to treat renal disease (which is known to be complicated by hypertension) with a reasonable expectation of success.

Applicants argue at p. 9, last paragraph through p. 10, 1st 3 paragraphs that the state of the art teaches away from combining ACE inhibitors with other agents, and cite evidence in the form of Adhiyaman et al., Murray et al. and Leary et al.

This argument has been fully considered but is not found persuasive. Adhiyaman et al. report neprotoxicity in the elderly due to combination of ACE inhibitors and non-steroidal anti-inflammatory drugs, or NSAIDs. However, it was common knowledge at the time of the invention that NSAIDs are associated with ***many*** side effects, even when taken on their own, including hypertension and kidney failure.

Adhiyaman et al. do not support an argument that the combination of ACE inhibitors and BMPs would be unsafe. Similarly the reference by Murray et al. does not support an argument that the combination of ACE inhibitors and BMPs would be contraindicated. Murray et al. report a case in which two renal transplant patients experience acute renal failure as a result of a combination of ACE inhibitors and cyclosporine, an immunosuppressant drug that is given to transplant patients. Nevertheless Murray et al. also point out at p. 66, left column, 1st paragraph that "[c]yclosporine can exert a toxic effect on the intrarenal vasculature." In other words, cyclosporine alone can have unwanted side effects upon the kidney. This does not instruct the person of ordinary skill in the art about side effects of ACE inhibitors or ACE inhibitors and BMPs. Finally, with regard to Leary et al., the authors teach that ACE inhibitor therapy (captopril and enalapril) is beneficial for counteracting diuretic induced hyperuricaemia (see abstract). The reference does not teach away from combination of ACE inhibitors with BMPs, but rather only teaches a clinical benefit of two specific ACE inhibitors.

Vukicevic et al. (of record) teach the benefits of BMPs. See, for example, p. 213, left column, last paragraph that OP-1 (a BMP) promotes renal repair and regeneration, improves kidney function, minimizes tubular necrosis and tissue infarction, suppresses inflammation and reduces programmed cell death, i.e., there are many beneficial effects of OP-1 that could be useful for treatment of renal disease. None of the prior art presented by Applicants provide evidence against the combination therapy of ACE inhibitors and BMPs, nor do they present evidence that BMPs are dangerous to the

kidney. The prior art of record ***does***, however, provide strong evidence of beneficial effects of OP-1 on renal function.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christina Borgeest whose telephone number is (571)272-4482. The examiner can normally be reached on 9:00am - 3:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker can be reached on 571-272-0911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Christina Borgeest

/Bridget E Bunner/
Primary Examiner, Art Unit 1647